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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,987	03/13/2001	Christian Waeber	M0765/7035 (ERG/MAT)	9309

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EXAMINER
LI, RUIXIANG

ART UNIT	PAPER NUMBER
1646	17

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/804,987	Applicant(s) WAEBER ET AL.	
	Examiner Ruixiang Li	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,43,56,88-91,93,96-99,101-105,108-111 and 113-139* is/are pending in the application.

4a) Of the above claim(s) *115-120, 132, 133, 135, 136, 138, and 139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,43,56,88-91,93,96-99,101-105,108-111,113,114,121-131,134 and 137* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

I. Status of Application, Amendments, and/or Claims

The amendment filed in Paper No. 16 on June 13, 2003 has been entered in full. Claims 86, 87, 92, 94, 95, 100, 106, 107, and 112 have been canceled. Claims 34, 43, 56, 88-91, 96-99, 105 and 108-111 have been amended. Claims 115-139 have been added. Claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, and 113-139 are pending. Claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113, 114, 121-131, 134, and 137 are under consideration. Newly added claims 115-120, 132, 133, 135, 136, 138, and 139 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

II. Withdrawn Objections and/or Rejections

The rejection of claim 105 under 35 U.S.C. 112, 2nd paragraph, as set forth at page 7 of the previous Office Action (Paper No. 14, March 11, 2003), has been withdrawn in view of Applicants' amendment to the claim.

III. Drawings

The formal drawings submitted on June 13, 2003 have been accepted by the Examiner.

IV. Information Disclosure Statement

The Information Disclosure Statement submitted on May 15, 2003 has been placed in the file. All except the reference of Salomone et al. (C19) has been considered by the Examiner. The information (month and year) on the reference of Salomone is missing. Without this information, the Examiner is unable to determine whether it can be used as a 102 (a) art or not.

V. Claim Rejections Under 35 U. S. C. § 112, 1st Paragraph (Enablement)

The rejection of claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113, and 114 under 35 U. S. C. § 112, 1st paragraph, as set forth at pages 3-5 in the previous office action (Paper No. 14, March 11, 2003), remains.

Newly added claims 121-131, 134, and 137 are also rejected under 35 U. S. C. § 112, 1st paragraph. The basis for the rejection has been set forth in paper No. 14.

Applicants argue that Applicants have shown that vasoconstriction was observed in cerebral arteries and coronary arteries to a lesser extent. Applicants submit that since Applicants' discovery, other groups have also confirmed the vasoconstrictive effects of S1P in non-cerebral arteries.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the specification (page 50, line 21-23) states that "By contrast, coronary arteries were weakly constricted, whereas carotid and femoral arteries were unresponsive". The specification also discloses that S1P is able to cause the selective constriction of cerebral arteries, but not normal peripheral arteries such as the femoral, carotid or coronary arteries (bottom of page 2; lines 13-14 of page

54). The specification further discloses that EDG3, as well as other EDG receptors, are expressed in other arteries that are non-responsive to S1P, including the coronary, carotid and femoral arteries (top of page 3). This indicates that factors in addition to EDG receptors are involved in the selective vasoconstriction of cerebral arteries (top of page 3). Applicants cannot ignore the instant disclosure and argue against the specification. Since the invention is drawn to a method of treatment with an agent that increases vasodilation or inhibition vasoconstriction, the claimed invention treating any arteries other than cerebral artery is not enabled, regardless of the potential mechanisms. Even applicants' own publication (Eur. J .Pharmacol. 2003 May 23;469(1-3):125-34) after filing date teaches that S1P selectively constricted isolated cerebral, but not peripheral arteries.

Secondly, the art cited by the applicants does not enable the instant invention. According to the Wands factors, the state of the art, the relative skill of those in the art, and the predictability or unpredictability of the art are all considered at the time when the instant application was filed, i.e., the effective filing date of the application. The art after the filing date of the application does not provide supporting evidence that the claimed invention is enabled.

More importantly, the claimed invention is drawn to a method for treating a subject having, or at risk of having, a disorder which can be treated by increased vasodilation or inhibition vasoconstriction, comprising administering to a subject in need of such treatment an agent that down-regulates S1P-bing EDG receptor signaling. However, the specification only discloses two EDG-3 receptor inhibitors, sphingosine

and suramin, which have different structures. The specification fails to teach how to make the broad genus of the agents or even EDG-3 receptor inhibitors other than sphingosine and suramin. The art cited by the applicants does not teach an agent that increases vasodilation or inhibition vasoconstriction.

Applicants argue that the experiments disclosed in the specification show that at least EDG-3 is involved in vasoconstriction with S1P, they do not preclude the involvement of other EDG receptors. Applicants submit that there are differences in the transduction pathways that regulate vasoconstriction and, therefore, other proteins may be involved in the vasoconstrictive transduction pathways of the S1P-binidng EDG receptors. Applicants further submit that the antisense experiment does not conclusively rule out the involvement of the EDG-5 receptor.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First and foremost, the specification only discloses two EDG-3 receptor inhibitors, sphingosine and suramin, that increases vasodilation or inhibits vasoconstriction. The specification fails to provide any information on any other EDG receptor inhibitors that increases vasodilation or inhibits vasoconstriction.

Secondly, the specification clearly states that edg-3 or edg-5 antisense specifically reduced the respective RT-PCR product by 80%-90%, and in the preparation treated with edg-3 antisense, the concentration-responsive curve to S1P was significantly shift to right. These experiments apparently exclude the involvement of EDG-5 receptors in mediating the vasoconstrictor response to S1P in cerebral blood vessels. While these experiments cannot exclude other EDG receptors in mediating the

vasoconstrictor response to S1P in cerebral blood vessels, they neither support involvement of other EDG receptors. To determine whether other factors are involved in the vasoconstrictive transduction pathways of S1P-binding EDG receptors would require undue experimentation, which is not allowed under 35 U. S. C. § 112, 1st paragraph. In this regard, it is noted that, as taught by the art (see, e.g., Ancellin et al. J. Biol. Chem. 274:18997-9002, 1999;) and also acknowledged in the specification (second paragraph of page 53), an EDG-3 inhibitor, suramin, does not antagonize EDG-5 receptors. This fact clearly weighs in favor of the Examiner's position that each EDG receptor has differential pharmacological properties and signaling characteristics and would be expected to function differently from EDG-3 receptor.

Applicants argue that additional evidence implicates other EDG receptors in vasoconstriction. Applicants' argument has been fully considered, but is not deemed to be persuasive because the art cited by applicants is after the effective filing date of the instant application. These references cannot be used to support applicants' argument that the claimed invention is enabled. Secondly, the publication referred by Applicants as Applicants own work is also involved other authors who are not inventors. The data or information contained in the publication is not in an appropriate form so that the examiner can examine the validity of the data or information. Finally, none of the information appears to address a method of treating a disorder by increased vasodilation or inhibition of vasoconstriction with an agent that down-regulates S1P-binding EDG receptor signaling.

Applicants argue that Applicants have amended claims 34, 43, and 56 to read on

the S1P-binding EDG receptors. The Examiner notes that the scope of the amended claims are narrower, but the claims still encompass S1P-binding EDG receptors other than EDG-3 receptor.

Finally, Applicants argue that with the guidance provided in the specification as well as the level of skill in the art, one of ordinary skill is able to determine any agents that function to downregulate S1P-binding vasoconstricting EDG receptor signaling. Applicants criticize that the Examiner has recited these enablement factors but has not analyzed each of them.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. The claims recite a genus of agents (or EDG receptor inhibitors), but the specification merely discloses two EDG-3 receptor inhibitors, which have different structures, increase vasodilation or inhibits vasoconstriction. As taught by the art (see, e.g., Ancellin et al. J. Biol. Chem. 274:18997-9002, 1999;) and also acknowledged in the specification (second paragraph of page 53), an EDG-3 inhibitor, suramin, does not antagonize EDG-5 receptors. The relative skill of those in the art at the time when the application was filed was not high. All the references recited by the Applicants are published after the effective filing date of the application. The specification fails to provide working examples or sufficient guidance regarding how to make the genus of the agents. It is noted that an assay for finding a product is not equivalent to a positive recitation of how to make a product. Due to the complexity of the nature of the invention, unpredictability of the art regarding the action of an agent, the specification fails to enable an artisan to practice the claimed

invention in commensurate in scope with these claims without undue experimentation. The examiner believes that the enablement factors have been carefully weighed in relation to the specification, as set forth in Paper No. 14 and noted above.

VI. Claim Rejection Under 35 U. S. C. § 112, 1st Paragraph (Written Description)

The rejection of claim 104 under 35 U.S.C. 112, 1st paragraph (Written Description), as set forth at pages 5-6 of the previous Office Action (Paper No. 14, March 11, 2003), remains.

Applicants argue that the term "neuroprotective agent" is a term of art such that one of ordinary skill in the art would recognize that Applicants had possession of the claimed invention. Applicants submit that a simple search of the PubMed database alone for the term "neuroprotective agents" found more than 21,000 articles reciting this term. Applicants further argue that the Examiner's ability to define the term neuroprotective agent speaks to the unambiguousness of the term.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the claim does not require that "a neuroprotective agent" possesses any specific activity, nor any particular structure, or other disclosed distinguishing feature. Thus, the scope of the claim is so broad that it encompasses any agents as long as they have activities that protect the nerve system, and as well as any agents to be discovered in the future. Clearly Applicants were not in possession the claimed invention.

Secondly, the wide use of the term, "neuroprotective agents" in the art does not convey that Applicants were in possession of the claimed invention. In fact,

Applicants have not disclosed representative species in the specification whereas the examples listed by the Applicants in the argument are structurally unrelated. Thus, Applicants are not entitled to the claimed genus of neuroprotective agents.

Furthermore, the specification even fails to disclose a single neuroprotective agent to treat a subject with a specific condition. Treatment of an unspecified condition with an identified neuroprotective agent fails to satisfy the requirement for written description under 35 U.S.C. §112, first paragraph.

Finally, the requirement for written description under 35 U.S.C. §112, first paragraph is different from the indefinite rejection under 35 U.S.C. §112, second paragraph. Thus, Applicants' argument about the unambiguousness of the term, "neuroprotective agents" is irrelevant to the rejection of claim 104 under 35 U.S.C. §112, first paragraph for written description.

VII. Claim Rejection Under 35 U. S. C. § 112, 2nd paragraph

The rejection of of claim 104 under 35 U.S.C. §112, 2nd paragraph, as set forth at page 7 of the previous Office Action (Paper No. 14, March 11, 2003), remains.

Applicants argue that one of skill in the art would understand the second agents encompassed by the claim as the term has been commonly used in the art. Applicants' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth in Paper No. 14.

VIII. Claim Objections

The objection of claims 89, 97, 104, and 109 for reciting unelected EDG receptor inhibitors, as set forth at page 7 in previous office action (Paper No. 14, March 11,

2003), remains because Applicants have not amended the claims to remove the unelected subject matter.

Newly added claims 115-120, 132, 133, 135, 136, 138, and 139 are also objected because they recite unelected EDG receptor inhibitors.

IX. Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
August 18, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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